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EDITORIAL COMMENT

Editorial Comment: Iron-sensitive MR imaging of the primary motor cortex to differentiate hereditary spastic paraplegia from other motor neuron diseases

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Key Points

- *Conventional and advanced MR techniques may aid in the diagnosis of motor neuron disease.*
- *Iron-sensitive MR imaging of the primary motor cortex may reveal changes to help differentiate hereditary spastic paraplegia (HSP) from UMM predominant amyotrophic lateral sclerosis (UMN-ALS) and primary lateral sclerosis (PLS).*
- *Additional research in this area is necessary.*

Keywords Hereditary spastic paraplegia · Primary lateral sclerosis · Amyotrophic lateral sclerosis · Magnetic resonance imaging · Primary motor cortex

Abbreviations

ALS	Amyotrophic lateral sclerosis
HSP	Hereditary spastic paraplegia
LMN	Lower motor neuron
PLS	Primary lateral sclerosis
UMN	Upper motor neuron

Motor neuron disease encompasses a spectrum of neurodegenerative disorders characterised by an upper motor neuron (UMN) and/or lower motor neuron (LMN) dysfunction. In patients with a predominant UMN phenotype, the major differential diagnosis includes hereditary spastic paraplegia (HSP), UMN predominant amyotrophic lateral sclerosis (UMN-ALS), and primary lateral sclerosis (PLS). Clinical differentiation between these three disorders can be challenging, often resulting in considerable diagnostic delays.

Classically, HSP is considered a hereditary disorder, and family history and molecular genetic testing are key in the diagnostic workup. However, verifiable family history may be absent and molecular genetic tests may not confirm the diagnosis in more than 50% of cases [1]. PLS is sporadic, and genetic testing can make a confirmatory diagnosis in less than 20% of ALS cases [2].

Neuroimaging research is rapidly evolving in the field of upper motor neuron disease. Increasing studies suggest that conventional and advanced MR techniques may have the potential to assist in characterisation to improve the differential approach. Thinning of the primary motor cortex on structural MRI has been reported to be a consistent feature in patients with ALS [3]. Voxel-based morphometry studies have suggested that grey matter loss may also extend to the frontal, parietal, and limbic regions [4]. In patients with PLS, focal atrophy of the pericentral gyri extending to the extra-motor areas has been reported in small case series, and in some cases linked to cognitive impairment [5]. Non-specific features of thinning of the corpus callosum and ventricular enlargement have also been described in HSP and other motor neuron diseases [6].

Patients with ALS have been observed to have signal intensity changes along the corticospinal tract, seen on T2-weighted, proton density (PD)-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences [7]. These have been noted as regions of signal hyperintensity from the centrum semiovale to the brain stem, most readily identified in the posterior limb of the internal capsule [8]. However, these findings are not sensitive or specific, occurring in variable frequency (ranging from 15 to 76%) in ALS and seen in normal subjects [7].

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On T2*-weighted imaging and susceptibility weighted imaging (SWI), a characteristic hypointense rim in the primary motor cortex has been observed in ALS [9]. Specifically, studies using ultra-high field MRI have shown the signal hypointensity to be localised to the deep layers of the primary motor cortex [10], pathologically thought to correspond to abnormal iron deposition from cortical microgliosis.

In this issue of *European Radiology*, Cosottini et al explore the iron-related signal changes of the primary motor cortex in patients with HSP, PLS, and UMN-ALS using targeted T2*-weighted imaging [11]. The authors uniquely investigate the T2* signal intensity of the primary motor cortex in HSP, which has not been assessed in previous works so far. The signal intensity of the primary motor cortex in HSP was directly compared with PLS, ALS, and UMN-ALS.

Notably, most HSP patients were found to have normal signal intensity in the primary motor cortex, and marked cortical hypointensity was uncommon in HSP (occurring in 14% of cases) but found to occur in the majority of PLS and UMN-ALS patients (occurring in 100% and 75% of cases respectively).

The findings raise questions regarding the potential interplay between iron and the different neurodegenerative processes underpinning HSP, PLS, and UMN-ALS, which may result in varying frequencies of cortical hypointensity in the primary motor cortex. With such significant differences in the occurrence of hypointensity in the primary motor cortex in HSP compared to PLS and UMN-ALS, we may speculate on the potential merit of the sign to differentiate HSP from PLS or UMN-ALS, in patients with motor neuron disease presenting with UMN syndromes.

Yet, iron deposition in the primary motor cortex is also not unique to motor neuron diseases. Decreased T2 signal intensity in the motor cortex has been identified in other normal and abnormal conditions, including normal ageing, and previous infarcts of the deep white matter and/or basal ganglia; previous histochemical studies additionally demonstrate cortical iron deposition with increasing age [12]. Therefore, there is potential that the findings may be subject to certain confounding (e.g., due to non-age-matched groups).

Remarkably, the study showed a much higher frequency of cortical hypointensity in patients with UMN-ALS compared to ALS. As UMN dysfunction is predominant in UMN-ALS, but may only be mild in ALS which typically has mixed UMN/LMN dysfunction, these findings support previous reports suggesting positive correlations between cortical hypointensity and ALS UMN burden [10].

Unfortunately, as with many motor neuron disease studies in the literature, this study is constrained by relatively small sample sizes. This may be attributable to the low prevalence of motor neuron diseases. Furthermore, the heterogeneity of the current HSP cohort limits separate analyses of the major genetic HSP subtypes. Future investigations should be aimed at validating the current findings in larger populations and clarifying the performance and utility of signal hypointensity in HSP and the spectrum of upper motor neuron diseases.

Overall, the current work certainly presents interesting additional insight into the evolving field of neuroimaging of motor neuron disease. Increasing efforts for early diagnosis of motor neuron disease underscore the need to determine reliable neuroimaging diagnostic markers, which can complement clinical and genetic testing. Future research in iron-sensitive MR imaging of the primary motor cortex will certainly shed further light on its potential clinical application in upper motor neuron disease.

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Declarations

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Methodology
• Editorial comment

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